Conjugated Systems Derived from Piperazine-2,5-dione

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The preparation of mono- and of symmetrical and unsymmetrical bis-ylidine derivatives of piperazine-2,5-dione is described. The uv-visible absorption of the products is correlated with acceptor/donor character of the substituents.

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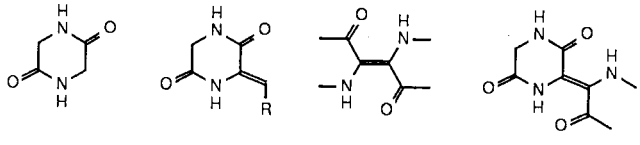
Introduction.

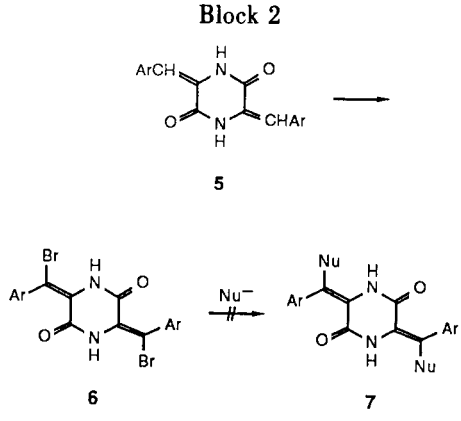
Block 1



1 2 3 4

The chemistry of piperazine-2,5-dione **1** is of interest since many natural products possess its ring system [1-3]. Derivatives of **1** are useful in peptide synthesis [2,4] and characterization [5], in the synthesis of pyrazines [6], and as 4π components for Diels-Alder reactions [7]. Compound **1** condenses readily with aromatic aldehydes [3,8] to give 3,6-bis(arylidene)piperazine-2,5-diones **5**. Reaction with aliphatic aldehydes requires more vigorous conditions and yields mono-alkylidene derivatives **2** [9]. Alternatively, compounds of type **2** have been prepared from acyclic starting materials [10]. Mixed arylidene(alkylidene)-piperazine-2,5-diones have been prepared from **2** and aromatic aldehydes under standard conditions [10-11]. These ylidene derivatives have been characterized spectroscopically [3], and have been chemically [8,12-13] and catalytically [13-14] reduced, brominated [12], and reacted with nucleophiles (Grignard reagents [12], sulfides [15-16]), and electrophiles [17]. Ketones have been reported not to react at all [9].

Block 2



5 6 7

Our attention was drawn to compounds of types **2**, **5**, and **14** because of their structural similarity to the chromophore **3** of indigo. We reasoned that if benzylidene derivatives could be obtained with donor-acceptor substitution (*cf.* **4**) then merostabilization of the excited state [18] should occur to afford deeply colored compounds that might be novel dyestuffs [19]. Our first approach to this class of derivative lay in the attempted preparation of (α-bromoarylidene)piperazine-2,5-dione **6** and by attempted reaction of these derivatives with various nucleophiles to give addition-elimination adducts **7**.

Benzylidene Derivatives.

Piperazine-2,5-dione **1** was prepared [4] by self-condensation of glycine in ethylene glycol in 28% yield. Reaction of **1** with benzaldehyde and with 2-nitrobenzaldehyde readily occurred in the presence of acetic anhydride and sodium acetate at 120-140° to give **5a** and **5i** in yields of 63% and 42%, respectively, as expected [12]. Contrary to the literature [8], attempted reaction of **1** with 2-pyridinecarboxaldehyde failed under these same conditions. However, by reacting 1,4-diacetylpiperazine-2,5-dione **9** [9,13] with 2- and 4-pyridinecarboxaldehyde in the presence of an equivalent of triethylamine with dimethylformamide as the solvent, the expected products were obtained in good yield (**5f**, 85% and **5g**, 88%). Their structures were deduced by elemental analysis and by ^{1}H nmr which showed a methine absorption from two protons at δ 6.53 (**5f**) and δ 6.80 (**5g**), and two absorptions in the aromatic region from pyridine ring protons.

Attempted conversion of piperazines **5** into tetrabromo-derivatives by bromination in hot glacial acetic acid [12] usually gave 3,6-bis(α-bromobenzylidene)piperazine-2,5-diones **6**, although such reactions of **5f** and **5g** with bromine gave what appeared to be salts of the dibromo-derivatives. Attempts to react **6** with various nucleophiles failed to give the expected products of type **7**.

The condensation of 1,4-diacetylpiperazine-2,5-dione **9** with aldehydes could easily be controlled to occur stepwise. Novel monoarylidene derivatives **14** were prepared

Scheme 1

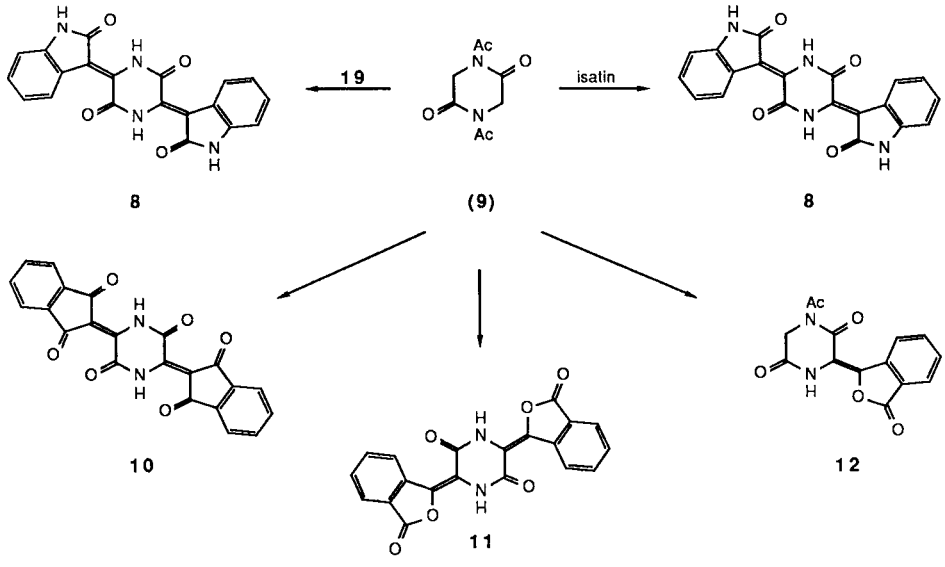


Table I

Preparation of Monoarylidene Piperazine Derivatives **14**

No.	Ar	Yield %	mp (°C)	lit mp (°C)	Calcd. C	Calcd. H	Calcd. N	Formula	Found C	Found H	Found N
14a	C_6H_5-	66	195-197	200-201 [11]	– –	– –	– –	$C_{13}H_{12}N_2O_3$	– –	– –	– –
14b	*p*-$CH_3C_6H_4$-	57	162-164	– –	65.12	5.43	10.85	$C_{14}H_{14}N_2O_3$	65.45	5.28	10.71
14c	*p*-$CH_3OC_6H_4$-	54	174-174	179-180 [11]	– –	– –	– –	$C_{14}H_{14}N_2O_4$	– –	– –	– –
14d	*p*-$O_2NC_6H_4$-	75	212-214	213-215 [11]	– –	– –	– –	$C_{13}H_{11}N_3O_5$	– –	– –	– –
14e	*m*-ClC_6H_4-	79	219-221	– –	56.01	3.95	10.05	$C_{13}H_{11}ClN_2O_3$	55.90	3.91	9.80
14f	2-C_5H_4N-	81	200-202	– –	58.88	4.49	17.14	$C_{12}H_{11}N_3O_3$	58.71	4.49	17.16
14g	4-C_5H_4N-	84	218-220	– –	58.88	4.49	17.14	$C_{12}H_{11}N_3O_3$	58.45	4.44	17.59
14h	*p*-$(CH_3)_2NC_6H_4$-	43	211-213	– –	62.72	5.92	14.63	$C_{15}H_{17}N_3O_3$	62.82	5.74	14.35

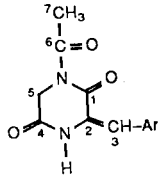
Table II

Spectra of Monoarylidene Piperazine Derivatives **14**

No.	Ar	ir (cm^{-1}) ν NH	ν $COCH_3$	ν C=O	ν C=C	^1H NMR (δ) NH	Ar-H		CH=C	CH_2	$COCH_3$	Other
14a	C_6H_5-	3250	1690	1620	1610	10.35	7.25-7.80		7.10	4.42	2.55	
14b	*p*-$CH_3C_6H_4$	3320	1690	1620	1600	10.35	7.60 (d, 2H)	7.31 (d, 2H)	7.08	4.42	2.57	2.39 (CH_3)
14c	*p*-$CH_3OC_6H_4$-	3300	1690	1630	1600	10.18	7.66 (d, 2H)	7.07 (d, 2H)	7.12	4.45	2.60	3.90 (OCH_3)
14d	*p*-$O_2NC_6H_4$-	3350	1700	1660	1620	10.90	8.52 (d, 2H)	8.00 (d, 2H)	7.16	4.50	2.60	
14e	*m*-ClC_6H_4-	3250	1690	1670	1630	10.75	7.70 (d, 1H)	7.3-7.6 (m, 3H)	7.02	4.43	2.55	
14f	2-C_5H_4N-	3250	1700	1660	1620	12.5	8.80 (m, 1H)	7.3-8.2 (m, 3H)	6.97	4.45	2.57	
14g	4-C_5H_4N-	3400	1690	1660	1620	10.81	8.80 (d, 2H)	7.65 (d, 2H)	7.08	4.58	2.62	
14h	*p*-$(CH_3)_2NC_6H_4$-	3350	1685	1650	1610	10.38	7.62 (d, 2H)	6.98 (d, 2H)	6.82	4.48	2.52	3.03 [$(CH_3)_2N$]

Table III

^{13}C NMR Spectra of Monoarylidene Piperazine Derivatives (**14**)

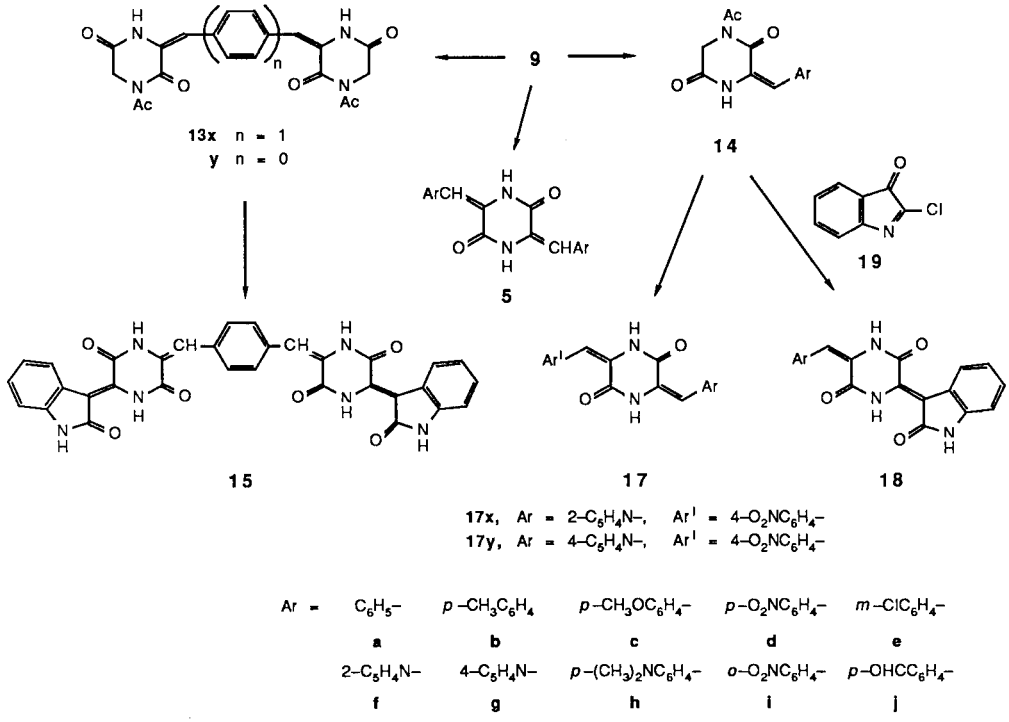


No.	C_1	C_2	C_3	C_4	C_5	C_6	C_7	Aromatic carbon signals	Other
14b	163.6	119.5	129.9	161.5	45.6	171.4	26.5	138.3, 129.4, 129.2, 125.7	20.9 (CH_3)
14e	163.9	117.0	130.1	161.1	45.5	171.5	26.6	135.0, 133.3, 128.8, 127.8, 120.5	
14f	165.2	109.8	129.6	161.5	48.3	174.9	28.7	152.4, 146.5, 144.7, 135.1, 126.7	
14g	163.9	114.9	129.8	160.7	45.6	171.6	26.6	149.7, 140.3, 123.4	
14h	164.1	120.2	131.5	159.5	45.4	171.1	26.4	122.3, 121.7, 111.7, 106.6	36.9 [$(CH_3)_2N$]

from the reaction of **9** with one equivalent of aromatic aldehydes in dimethylformamide and with triethylamine as base. They were characterized analytically, and by their ^1H and ^{13}C, and ir spectra (Tables I-III). These monoarylidene derivatives **14** could be further condensed with different aromatic aldehydes under the same conditions to afford unsymmetrical 3,6-diarylidenepiperazine-2,5-diones **17**. In this way, 3-(2-pyridylmethylidene)-6-(4-nitribenzylidene)piperazine-2,5-dione **17x** and 3-(4-pyridylmethylidene)-6-(4-nitrobenzylidene)piperazine-2,5-dione **17y** were prepared in good yields (Scheme 2).

Reaction of **9** with ninhydrin produced the dark brown bis-derivative **10** (Scheme 1) (54%), which was characterized analytically and by its ir spectrum. When **9** was reacted with terephthaldicarboxaldehyde, the structure of the yellow product was dependent on the ratio of substrates. A 1:2 ratio of **9** to dialdehyde gave **5j**, which showed an NH absorption at 3240 cm^{-1} and broad bands at 1680 cm^{-1} for the carbonyl group and 1630 cm^{-1} for the aliphatic C=C group. In the ^1H nmr spectrum, signals were observed for the aldehyde proton, for the aromatic protons (two doublets), and for the CH proton (a singlet). A

Scheme 2



2:1 ratio of **9** to dialdehyde afforded **13x** (Scheme 2), the ^{1}H nmr of this revealed methyl groups at δ 2.86 (6H), methylene signals at δ 4.93 (4H), and singlets at δ 7.73 and δ 7.83 for the CH and aromatic protons, respectively. The ir spectrum showed an NH absorption at 3210 cm^{-1} and two intense bands at 1670 (broad) and 1620 cm^{-1}. The reaction of **9** and glyoxal carried out under the same conditions gave **13y** as a brownish solid (Scheme 1). Structure **13y** was deduced by its elemental analysis and from the ir spectrum which showed an NH absorption at 3150 cm^{-1} and three carbonyl bands at 1700, 1660 and 1620 cm^{-1}.

Reaction of 1,4-diacetylpiperazine-2,5-dione with phthalic anhydride produced two different products depending the reaction temperature. Thus, the monocondensation product 1-acetyl-3-(3-oxophthalylidene)-piperazine-2,5-dione **12** was obtained in 38% yield by stirring **9** with phthalic anhydride in dimethylformamide and triethylamine as a base at 25°; the bis-condensation product 3,6-di(3-oxophthalylidene)piperazine-2,5-dione **11** was formed (30%) in a similar manner but with stirring at 90° (Scheme 1).

Indolylidene Derivatives.

Failure of these attempts to convert the 3,6-bis(α-bromoarylidene)piperazine-2,5-diones by addition-eliminations with various nucleophiles prompted us to look for other ways to synthesize new donor-acceptor substituted methylidenepiperazine-2,5-dione. Novel piperazine-2,5-dione derivatives were prepared by the reactions of di- or monoacetylpiperazine-2,5-diones with 2-chloroindol-3-one **19**. 2-Chloroindol-3-one **19** has previously been used to synthesize indigo type dyestuffs [20] by reactions with amines or diamines [21-22], phenols or naphthols [23], or hydantoins [24].

1,4-Diacetylpiperazine-2,5-dione **9** reacted readily with 2-chloroindol-3-one **19** at room temperature in dimethylformamide with triethylamine as a base to give the bis-indolyl derivative **8** as a purple solid. Surprisingly, the structure of this bis-indolyl derivative is 3,6-di-(2-oxo-3-indolylidene)piperazine-2,5-dione (and not the expected 3-oxo-2-indolylidene isomer, indigo analogue) as shown by comparing its melting point, ir spectrum and visible ab-

Table IV

Preparation of Indolylidene Derivatives **18**

No.	Ar	Yield (%)	mp (°C)	Calcd. C	Calcd. H	Calcd. N	Formula	Found C	Found H	Found N
18a	C_6H_5-	51	306-308	68.80	3.93	12.69	$C_{19}H_{13}N_3O_3$	68.49	4.00	12.30
18b	p-$CH_3C_6H_4$-	71	297-299	69.54	4.35	12.14	$C_{20}H_{15}N_3O_3$	69.38	4.46	11.87
18c	p-$CH_3OC_6H_4$-	78	263-265	66.48	4.16	11.63	$C_{20}H_{15}N_3O_4$	66.25	4.47	11.58
18d	p-$O_2NC_6H_4$-	90	>300	60.54	3.17	14.89	$C_{19}H_{12}N_4O_5$	60.19	3.20	14.47
18e	m-ClC_6H_4-	66	290-292	62.38	3.28	11.49	$C_{19}H_{12}ClN_3O_3$	61.89	3.28	11.05
18f	2-C_5H_4N-	56	>320	65.06	3.64	16.86	$C_{18}H_{12}N_4O_3$	65.06	3.63	16.83
18g	4-C_5H_4N-	61	>320	65.06	3.64	16.86	$C_{18}H_{12}N_4O_3$	64.96	3.85	16.75

Table V

Spectra of Indolylidene Derivatives **18**

No.	Ar	IR (cm^{-1}) ν NH	ν C=O	ν C=C	^{1}H NMR (δ, dimethylsulfoxide-d_6) NH	Ar-H, CH=C
18a	C_6H_5	3190	1690, 1660	1615	8.80, 10.9, 11.4	5.9-7.9 (m)
18b	p-$CH_3C_6H_4$-	3200	1685, 1660	1615	8.88, 10.8, 11.1	6.7-7.8 (m) [a]
18c	p-$CH_3OC_6H_4$-	3200	1665, 1625	1600	8.88, 11.5, 12.8	6.9-7.9 (m) [b]
18d	p-$O_2NC_6H_4$-	3200	1680, 1660	1615	8.90, 11.5 (brs, 2H)	6.9-7.8 (m, 5H), 7.9 (d, 2H), 8.3 (d, 2H)
18e	m-ClC_6H_4-	3300	1690, 1660	1620	8.85, 11.2, 12.9	6.92-7.90 (m)
18f	2-C_5H_4N-	3190	1680, 1660	1620	not soluble	
18g	4-C_5H_4N-	3250	1690, 1650	1620	10.3, 12.2	6.9-8.9 (m, 10H) [c]

[a] 2.35 ppm (s, 3H, CH_3). [b] 3.90 ppm (s, 3H, OCH_3). [c] One NH group was overlapped here.

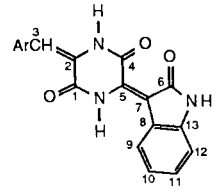
sorption with that of the product obtained from the reaction of 1,4-diacetylpiperazine-2,5-dione and isatin itself (Scheme 1). This reaction will receive further attention.

In the same way, reaction of **19** with **13x** gave product **15** in 84% yield (Scheme 2). Similar reactions were also carried out with a variety of the 1-acetyl-3-arylidenepiperazine-2,5-diones (**14, a-g**). The red products (**18, a-g**) were obtained in good yield (51-90%), and characterized analytically by their ^1H and ^{13}C nmr and ir spectra (Table IV-VI). Although these indolylidene derivatives could also be produced from the reaction of 1-acetyl-3-arylidenepiperazine-2,5-diones with isatin, 2-chloroindol-3-one is more reactive and gives much better yields.

These indolylidenes produced by reactions of acetylpiperazine-2,5-diones and 2-chloroindol-3-one are expected to be deeply colored due to merostabilization of the excited state; however, the color of the 2-oxo-3-indolylidene may not be as deep as that of the 3-oxo-2-indolylidene isomers because the latter possess the partial indigo structure. In ethanol or in dimethylformamide, most of these derivatives formed yellow solutions and showed an absorption around 400 nm (Table VII). This is not in agreement with the much darker color of the solid state and in concentrated solution; indeed solid state uv/visible spectra obtained in potassium bromide discs disclosed absorption above 500 nm, albeit, with much reduced extinc-

Table VI

^{13}C NMR Spectra of Indolylidene Derivatives (**18**)



No.	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8-C_{13}	Aryl group
18a	157.1	117.0	129.1	156.5	86.7	109.8	171.3	140.5, 136.2, 128.7, 127.0, 121.0, 120.5	139.4, 130.2, 127.7, 123.0
18b	157.5	117.0	129.8	156.4	86.7	109.8	171.2	140.4, 135.9, 129.0, 127.5, 121.5, 120.6	138.5, 124.6, 121.5, 108.1, 21.0 (CH_3)
18c	157.4	116.9	128.7	156.1	86.4	109.5	171.1	140.2, 135.5, 128.7, 126.6, 121.2, 120.4	131.2, 125.0, 123.3, 121.2, 55.1 (OCH_3)
18d	156.7	113.1	128.9	156.3	108.9	109.4	170.9	140.4, 134.6, 128.9, 127.1, 121.2, 120.2	139.4, 130.2, 127.7, 123.0
18e	157.1	114.6	129.0	156.3	86.4	109.5	171.0	140.4, 135.2, 128.7, 127.3, 121.3, 120.3	133.1, 130.0, 128.0, 126.1, 121.3, 114.6
18g	158.2	118.6	129.3	157.0	88.8	108.9	176.5	140.7, 135.3, 129.3, 128.5, 126.9, 121.6	149.6, 143.8, 129.3

Table VII

Visible Spectra of Bis-Ylidene Derivatives of Piperazine-2,5-dione in Solid State and in Solutions

	Solid state [a]		Ethanol solution [b]		Dimethylformamide solution	
No.	λ (ε)	λ [ε]	λ [ε]	λ [ε]	λ [ε]	λ [ε]
8	570 (2400)	469 (3500)	480 (17200)	422 (22900)	475 (17300)	425 (22000)
18a	517 (1060)	475 (1680)		380 (18200)		
18b	510 (1330)	468 (1900)	470 (15700)	394 (21800)		389 (25600)
18c	515 (1420)	480 (1850)		396 (18400)		
18d	530 (2100)	485 (2400)	475 (sh)	397 (22300)	546 (36500)	390 (25800)
18e	522 (1600)	480 (1800)	460 (sh)	386 (22000)	460 (10200)	378 (19200)
18f	520 (1750)	478 (1800)	460 (sh)	388 (49300)		
18g	512 (1600)	470 (2000)	465 (sh)	388 (43400)	450 (32300)	378 (66000)
15	545 (2500)	450 (1650)	550 (21000)	400 (26300)	440 (27800)	

[a] In potassium bromide disc (about 100 mg potassium bromide and 1 mg sample), with diameter 12 mm. [b] Concentration *ca.* 4 x 10^{-5} *M*. [c] Concentration *ca.* 4 x 10^{-5} *M*.

tion coefficients (Table VII). This behavior points to some special kind of association in the solid state, and we plan an X-ray investigation of this phenomenon.

EXPERIMENTAL

Melting points were measured on a Kofler Hot-Stage and were uncorrected. The ^1H nmr and ^{13}C nmr were obtained on Varian EM 360 L (60 MHz) and JEOL JNM FX 100 (25 MHz) spectrometers, respectively, chemical shifts (δ) are recorded downfield of tetramethylsilane as an internal standard unless otherwise noted. The ir spectra were recorded on a Perkin Elmer 283 spectrometer. The visible spectra were determined on a Perkin-Elmer 330 spectrophotometer.

The following compounds were prepared by the literature methods cited: 1,4-diacetylpiperazine-2,5-dione **9**, mp 98-100° (lit [13] mp 99.0-100.5°); 3,6-dibenzylidenepiperazine-2,5-dione **5a**, mp 297-299° (lit [25] mp 298-300°); 3,6-di(α-bromobenzylidene)piperazine-2,5-dione **6a**, mp 324-325° dec (lit [12] mp 321°); and 2-chloroindol-3-one **19**, mp 176-178° (lit [26] mp 180°).

3,6-Di(2-nitrobenzylidene)piperazine-2,5-dione (**5i**).

A mixture of 1.14 g (10 mmoles) of piperazine-2,5-dione, 3.0 g (20 mmoles) of 2-nitrobenzaldehyde, 3.3 g (40.2 mmoles) of anhydrous sodium acetate, and 6.9 ml (7.46 g, 73.1 mmoles) of acetic anhydride was heated at 130-140° until a solid cake had formed (4 hours). The mixture was washed with hot water, filtered, and further washed with small amounts of ethyl ether and acetone to give 1.6 g (42%) of **5i** as yellow powder, mp >340°.

Anal. Calcd. for $C_{18}H_{12}N_4O_6$: C, 56.84; H, 3.18; N, 14.73. Found: C, 57.00; H, 3.15; N, 14.56.

3,6-Di(2-pyridylmethylidene)piperazine-2,5-dione (**5f**).

A solution of 4.0 g (20.2 mmoles) of 1,4-diacetylpiperazine-2,5-dione, 3.82 ml (4.30 g, 40 mmoles) of 2-pyridinecarboxaldehyde, and 5.6 ml (7.8 g, 77.5 mmoles) of triethylamine in 40 ml of dimethylformamide was stirred at 25° overnight. The resulting precipitate was filtered off and washed with water and ethyl ether to give 5.0 g (85%) of **5f** as a yellow powder. Recrystallization from chloroform gave **5f** as yellow needles: mp >300° (lit [8] mp >300°); ^1H nmr (trifluoroacetic acid): 6.53 (s, 2H, CH=), 7.33 (m, 4H, Py-H), 7.93 (m, 4H, Py-H).

Anal. Calcd. for $C_{16}H_{12}N_4O_2$: C, 65.74; H, 4.14; N, 19.17. Found: C, 65.40; H, 3.81; N, 18.91.

3,6-Di(4-pyridylmethylidene)piperazine-2,5-dione (**5g**).

Preparation as above gave **5g** (88%) as a light-orange powder, mp >300°; ^1H nmr (trifluoroacetic acid): 6.80 (s, 2H, CH=), 7.63 (d, J = 6 Hz, 4H, Py-H), 8.33 (d, J = 6 Hz, 4H, Py-H).

Anal. Calcd. for $C_{16}H_{12}N_4O_2$: C, 65.74; H, 4.14; N, 19.17. Found: C, 65.67; H, 4.16; N, 19.19.

3-(2-Pyridylmethylidene)-6-(4-nitrobenzylidene)piperazine-2,5-dione (**17x**).

A mixture of 0.61 g (2.5 mmoles) of 1-acetyl-3-(2-pyridylmethylidene)-piperazine-2,5-dione **14f**, 0.75 g (5 mmoles) of 4-nitrobenzaldehyde and 0.51 g (5 mmoles) of triethylamine in 20 ml of dimethylformamide was stirred at 25° for 24 hours. The precipitate was filtered and washed with water and ethanol to give 0.56 g (71%) of **17x** as a yellow powder, mp >320°; ^1H nmr (trifluoroacetic acid): 7.5-9.0 (m, Ar-H and CH=); ir (bromoform): 3250 (NH), 1680 (C=O), 1630, 1590, 1500 and 1330 cm^{-1}; uv/vis (ethanol): 374 nm (9700).

Anal. Calcd. for $C_{16}H_{12}N_4O_4$: C, 60.71; H, 3.57; N, 16.76. Found: C, 61.02; H, 3.65; N, 16.76.

3-(4-Pyridylmethylidene)-6-(4-nitrobenzylidene)piperazine-2,5-dione (**17y**).

Preparation as above, yellow microcrystals, yield 69%, mp >320°; ^1H nmr (trifluoroacetic acid): 7.4-9.1 (m, Ar-H and CH=); ir (bromoform): 3250, 1680, 1625, 1400 and 1340 cm^{-1}; uv/vis (ethanol): 356 nm (31300); 420 nm (4500).

Anal. Calcd. for $C_{16}H_{12}N_4O_4$: C, 60.71; H, 3.57; N, 16.67. Found: C, 60.28; H, 3.59; N, 16.31.

3,6-Di(2-oxo-3-indolylidene)piperazine-2,5-dione (**8**).

A mixture of 0.99 g (5 mmoles) of 1,4-diacetylpiperazine-2,5-dione, 1.65 g (10 mmoles) of 2-chloroindol-3-one and 1.1 g (11 mmoles) triethylamine in dimethylformamide was stirred at 25° for 4 hours. The purple precipitate was separated by filtration and washed with ethanol to give **8** (91%), mp >300°; ir (bromoform): 3200 (NH), 1680 (C=O), 1660 (C=O), 1615 (C=C), 1430, 830 cm^{-1}; uv/vis (ethanol): 480 (17200), 422 (22900).

Anal. Calcd. for $C_{20}H_{12}N_4O_4$: C, 64.51; H, 3.22; N, 15.05. Found: C, 64.43; H, 3.51; N, 14.90.

Compound **8** was also prepared in 100% yield by the condensation of 1,4-diacetylpiperazine-2,5-dione with isatin under the similar conditions.

3,6-Di(1,3-dioxo-2-indanylidene)piperazine-2,5-dione (**10**).

A mixture of 0.99 g of 1,4-diacetylpiperazine-2,5-dione, 1.78 g (10 mmoles) of ninhydrin and 1.02 g (10 mmoles) triethylamine in dimethylformamide was stirred at 25° for 10 hours, then cooled to 0°. The resulting precipitate was filtered off, washed with ethyl ether and recrystallized from ethanol to give 1.08 g (54%) of **10** as a dark brown powder, mp >300°; ir (bromoform): 3200, 1690, 1660, 1610 and 1510 cm^{-1}.

Anal. Calcd. for $C_{22}H_{10}N_2O_6$: C, 66.35; H, 2.51; N, 7.02. Found: C, 66.58; H, 2.63; N, 6.48.

3,6-Di(4-carboxybenzylidene)piperazine-2,5-dione (**5j**).

Preparation as above, except the mixture was stirred at 25° for 2 hours and washed with water and hot acetic acid, gave **5j** (100%); mp >300°; ^1H nmr (trifluoroacetic acid): 7.63 (s, 2H), 7.90 (d, J = 7 Hz, 4H), 8.40 (d, J = 7 Hz, 4H), 9.33 (s, CHO); ir (nujol): 3200 (NH), 1680 (C=O), 1630 (C=C) cm^{-1}.

Anal. Calcd. for $C_{20}H_{14}N_2O_4$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.07; H, 4.25; N, 8.25.

4-Phenylenebis(ylidenepiperazine-2,5-dione) (**13x**).

Preparation as above, except the product was washed with water and ethanol, gave **13x** (55%); mp >300°; ^1H nmr (trifluoroacetic acid): 2.86 (s, 6H, $COCH_3$), 4.93 (s, 4H, CH_2), 7.83 (s, 4H, ArH); ir (nujol): 3210 (NH), 1670 (C=O, br), 1620 (C=C) cm^{-1}.

Anal. Calcd. for $C_{20}H_{18}N_4O_6$: C, 58.53; H, 4.42; N, 13.65. Found: C, 58.69; H, 4.38; N, 12.46.

Ethylenebis(ylidenepiperazine-2,5-dione) (**13y**).

Preparation as above, brownish powder, yield 57%, mp >300°; ir (bromoform): 3150 (NH), 1700 (C=O), 1660 (C=O), 1620 (C=C), 1600 cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}N_4O_7$: C, 47.72; H, 4.55; N, 15.90. Found: C, 47.56; H, 4.46; N, 15.76.

1-Acetyl-3-(3-oxophthalylidene)piperazine-2,5-dione (**12**).

A solution of 1,4-diacetylpiperazine-2,5-dione (1 g, 5 mmoles), phthalic anhydride (1.48 g, 10 mmoles) and triethylamine (1.4 ml) in dimethylformamide (35 ml) was stirred at 25° for one day. The precipitate was collected by filtration. Recrystallization from water gave 0.55 g (38%) of **12** as yellow needles, mp 263-264° dec; ^1H nmr (dimethyl sulfoxide-d_6): 2.58 (s, 3H, $COCH_3$), 4.38 (s, 2H, CH_2), 7.75-7.95 (m, 2H), 8.0-8.15 (m, 2H), 10.05 (br s, 1H, NH); ir (nujol): 3180 (NH), 1800 (C=O), 1720 (C=O), 1690 (C=O), and 1600 (C=C) cm^{-1}; uv/vis (ethanol): 352 (12000).

Anal. Calcd. for $C_{14}H_{10}N_2O_5$: C, 58.74; H, 3.52; N, 9.79. Found: C, 58.88; H, 3.38; N, 9.46.

3,6-Di(3-oxophthalylidene)piperazine-2,5-dione (**11**).

Preparation as above, except the stirring was carried out at 90°, yellow powder (30%), mp >300°; ir (nujol): 3180 (br, NH), 1790 (C=O), 1690 (C=O) and 1630 (C=C) cm^{-1}; uv/vis (ethanol): 420 nm (9200).

Anal. Calcd. for $C_{30}H_{10}N_2O_6$: C, 64.17; H, 2.69; N, 7.49. Found: C, 63.72; H, 2.75; N, 7.65.

1,4-Bis[6-(2-oxo-3-indolylidene)piperzine-2,5-dione)-3-ylidenemethyl]-benzene (**15**).

A mixture of 1.05 g of **13x** and 0.80 g of 2-chloroindol-3-one **19** was heated at 100° and stirred for 5 hours in dimethylformamide and triethylamine as the base. The whole was cooled and poured into water, filtered and washed with ethanol to give 1.22 g **15** as a red powder, mp >300°; ir (bromoform): 3250 (NH), 1675 (C=O), 1645 (C=C), 1610 (C=C), 1590, 970 and 810 cm^{-1}.

Anal. Calcd. for $C_{32}H_{20}N_6O_6 \cdot H_2O$: C, 63.79; H, 3.64; N, 13.92. Found: C, 63.80; H, 3.60; N, 13.63.

Monoarylidene Derivatives **14a-h**.

1,4-Dicacetylpiperazine-2,5-dione (20 mmoles), the corresponding aryl-aldehyde (20 mmoles) and triethylamine (20 mmoles) was stirred at 25° in dimethylformamide for 4-8 hours (*cf.* ref [11]). The resulting precipitate was filtered off and washed with water. Recrystallization from ethanol or methanol gave pure monoarylidene derivatives **14a-h**, (Table I).

3-(2-oxo-3-indolylidene)-6-arylidene Derivatives **18a-g**.

2-Chloroindol-3-one **19** (10 mmoles), the appropriate 1-acetyl-3-aryl-methylidenepiperazine-2,5-dione (10 mmoles) and triethylamine were stirred in dimethylformamide at 25° overnight. The reaction mixture was poured into water; the resulting precipitate was filtered off and washed with water and ethanol to give the desired products (Table IV).

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